REMARKS/ARGUMENTS

By this amendment, applicants have amended Claims 17-19, and added new claims 20-72. Applicants respectfully submit that the amendments to the claims and the new claims are supported by the specification as originally filed. For example, isoform-specific antibodies can be found at Example 6 of the present specification (page 21, line 24 *et seq.*), as well as the following patent documents incorporated by reference. Specifically, at page 5, lines 22-25, the current application incorporates by reference the entire disclosures of U.S. Pat. Nos. 5,840,693 and 5,607,918, and WO 98/07832.

In U.S. Pat. No. 5,840,693, it is provided at Column 5, line 6 et seq. that:

> [A]nother aspect of the invention involves providing a vector comprising an anti-sense nucleotide sequence which is complementary to at least a part of the DNA sequences disclosed herein which encode the new growth factor of the invention which promotes proliferation of endothelial cells. According to a yet further aspect of the invention such a vector comprising an anti-sense sequence may be used to inhibit, or at least mitigate, VEGF-B expression. The use of a vector of this type to inhibit VEGF-B expression is favored in instances where VEGF-B expression is associated with a disease such as in instances where tumors produce VEGF-B in order to provide for angiogenesis. Transformation of such tumor cells with a vector containing an anti-sense nucleotide sequence would suppress or retard angiogenesis and so would inhibit or retard growth of the tumor.

At Col. 30, line 26 – Col. 31, line 4:

> As demonstrated in Example 7, VEGF-B protein also can be used to produce antibodies. In general, conventional antibody production techniques may be used to produce VEGF-B antibodies. For example, specific monoclonal antibodies may be produced via immunization of fusion proteins obtained by recombinant DNA expression.
>
> Labeled monoclonal antibodies, in particular, should be useful in screening for conditions associated with abnormal levels of VEGF-B in the body. For example, an

> assay of VEGF-B in synovial fluids and/or joint tissue by immunofluorometric techniques analogous to the the procedure described by Fava et al., Journal of Experimental Medicine, 180:341-46 (1994) may be useful as a diagnostic indicator of rheumatoid arthritis. A radioimmunoassay of VEGF-B in occular fluid using techniques described by Aiello et al., in New England Journal of Medicine, 331(22) :1480-87 (1994) may be useful as a diagnostic indicator of diabetic retinopathy, neovascularization of the iris or retinal vein occlusion. Immunoassays of VEGF-B levels in blood, urine or other bodily fluids may be useful also as a tumor marker; see Kondo et al., supra. These monoclonal antibodies to VEGF-B also may be useful in inhibiting angiogenesis associated with high levels of VEGF-B in the body, e.g. in rapidly proliferating, angiogenesis-dependent tumors in mammals, and thereby may retard the growth of such tumors. Treatment with a monoclonal antibody specific for VEGF-B using techniques analogous to those described by Kim et al., in Nature, 362(6243) :841-44 (1993) may be useful to suppress or inhibit tumor growth in vivo. Intravenous and/or subcutaneous injection of monoclonal antibodies to VEGF-B using procedures like those described by Asano et al., in Cancer Research, 55:5296-5301 (1995) may be useful to inhibit neovascularization and primary and metastatic growth of solid tumors. For the therapy of humans, [chimerization] or humanization of such monoclonal antibodies is to be preferred. Treatment may be effected, e.g., by twice weekly intraperitoneal injection of 10 to 500 .mu.g, preferably 50-100 .mu.g of monoclonal antibody.
>
> VEGF-B antagonists such as antibodies also may be useful to inhibit new blood vessels in diabetic retinopathy, psoriasis, arthopathies and/or vascular tumors such as haemangiomas; see Aiello et al., *supra*.

In addition, page 9, line 29 - page 10, line 20 of WO 98/07832 provides a detailed discussion of VEGF-D antagonists, and at page 11, line 26 – page 12, line 22, it provides a discussion of method for inhibiting angiogenesis with antagonists in general, and antibodies in particular.

Accordingly, entry of the above claim amendments and favorable consideration thereof are respectfully requested.

If there are any questions regarding this preliminary amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket # 029065.48885D1).

Respectfully submitted,

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